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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1654	

MAIL DATE	DELIVERY MODE
11/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,222	FERGUSON ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 23-26* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *notice to comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/17/08 has been entered.

Applicant's amendment to claims in the response filed on 8/5/08 has been acknowledged.

Claims 1-7 and 23-26 are pending.

Claims 6 and 7 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/16/07.

Claims 1-5 and 23-26 have been examined on the merit.

Any objections and/or rejections made in the previous office action dated 3/18/08 not specifically mentioned here are considered withdrawn.

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821-1.825 for

the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to effect a complete response to this office action.

Specifically, Claims 5, 6 and specification on page 22 contains peptide sequences that requires SEQ ID NOs.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 23, 25 and 26 remain rejected under 35 USC 102(b) as being anticipated by Canadian patent application CA 2312109 of Dubois in light of the definition available from website:

"http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920", as stated for claims 1-3 in the previous office action dated 6/22/07 and reiterated below in the modified form to meet the limitations of claims as amended. Please note that response to applicant's argument follows the reiterated rejection.

In the instant application, applicants claim a method for reducing scar formation during the healing of at least one wound in a subject who has incurred injuries or in a subject who will

be inflicted with at least one surgical wound at a known site, comprising applying a furin inhibitor **directly** to the site of a wound, wherein said furin inhibitor inhibits TGF-β activation.

Dubois discloses a protein-based protease inhibitor that is a mutant of serpin α1-antitripsin wherein the reactive site has Arg-Ile-Pro-Arg^{358} sequence (known as PDX). This mutant has been shown to be a potent furin inhibitor (page 5, paragraph 2). Dubois also discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and abnormal wound healing, degenerative cartilage loss following traumatic joint injury and arthritis and others (Page 8, paragraph 2). Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC%/6 or PC7 (page 8, paragraphs 1 and 2). This meets the limitations of claims 1, 2 and 23. The reference also discloses pharmaceutical composition of that includes compositions with viscous paraffin, fatty acid mono and diglycerides (page 13, paragraph 1) and use of non-aqueous vehicles such as cottonseed oil and other oils (page 14, paragraph 1) that are useful in solubilizing lipid soluble active agents. This meets the limitations of claim 3. Dubois teaches the use of PDX or a construct, variant, analog, peptide, peptidomimetic, salt complex derivative thereof for abnormal wound healing with furin or furin-like inhibitors, therefore, it inherently reduces **scar formation** during healing of wounds (page 8, paragraphs 1 and 2). Dubois also discloses that the aforementioned pharmaceutical composition may be administered orally parenterally, inhalation, rectally or topically (page 12, paragraph 2). According to the definition available for "topical" in the website:

http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920, the term "topical" means "[d]escribes drugs or medications that are applied **directly** to the surface of the part of the body being treated". Hence meets the limitations of instant claims 1, 25 and 26. Therefore, the claims 1-3 and 25-26 of instant application are anticipated by Dubois.

Response to Arguments

1. Applicants argue that "[T]he bridging paragraph of pages 12-13 discusses topical administration among others but fail to suggest application directly to wound and in short, in the five or six pages devoted to techniques for administration starting on page 13 and continuing to page 16 of Dubois, applicants are unable to find any nexus between treatment of abnormal wound healing and any administration directly to the site of the wound. In view of this failure, Dubois falls short of the legal requirements for a finding of anticipation. In order to anticipate, each and every element of the claimed invention must not only be found in the cited document, the elements must be arranged and connected as described in the claim".

Applicant's arguments filed 8/5/08 have been fully considered but they are not persuasive. Dubois discloses pharmaceutical compositions of furin or furin-like inhibitors for treating abnormal wound healing and discloses that the composition may be administered topically as illustrated in the rejection above. Also, the dictionary definition for "topical" as evidenced by the website reference "http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920"

clearly illustrates the fact that topical application means direct application to the site, and in this case it is to the site of injury.

2. Applicants by quoting the case law of *Daiichi Pharmaceutical Co. v. Apotex, 83 USPQ2d 1471 (DCNJ 2006)* allege that Dubois reference is a 'piecemeal' interpretation of the instant invention. Applicants further state "[t]here is insufficient specificity in the teachings of Dubois to lead the reader to understand that in order to reduce scarring, a furin inhibitor should be applied directly to the wound. Accordingly, this basis for rejection may properly be withdrawn".

Applicant's arguments filed 8/5/08 have been fully considered but they are not persuasive. It should be noted that the instant specification is inadequate to support the claims as recited because, the specification does not provide any working examples wherein the furin or furin-like inhibitors are directly applied to wound site or to a site that would be affected by impending surgery. Hence the specification as disclosed does not support the claims as recited commensurate with the scope of the claims. As mentioned above, Dubois teaches topical application of furin or furin-like inhibitors that meets the limitations of instant claims. Moreover, the dictionary definition for "topical" as evidenced by the website reference: "http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920" clearly illustrates the fact that topical application means direct application to the site, and in this case it is to the site of injury.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4 and 5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Dubois in light of the definition available from website: "http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920", as applied to claims 1-3, 23, 25 and 26 above and further in view of Pearton, et al., 2001, Exp Dermatology, 10, 193-203, as stated previous office action dated 6/22/07 and reiterated below in the modified form to meet the limitations of claims as amended. Please note that response to argument follows the reiterated rejection.

In the instant application, applicants claim a method for reducing scar formation during the healing of at least one wound in a subject who has incurred injuries or in a subject who will be inflicted with at least one surgical wound at a known site, comprising applying a furin inhibitor **directly** to the site of a wound, wherein said furin inhibitor inhibits TGF-β activation.

Dubois discloses a protein-based protease inhibitor that is a mutant of serpin α1-antitripsin wherein the reactive site has Arg-Ile-Pro-Arg^{358} sequence (known as PDX). This mutant has been shown to be a potent furin inhibitor (page 5, paragraph 2). Dubois also discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and abnormal wound healing, degenerative cartilage loss following traumatic joint injury and arthritis and others (Page 8, paragraph 2). Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC%/6 or PC7 (page 8, paragraphs 1 and 2). This meets the limitations of claims 1, 2 and 23 (Page 8, paragraph 2). Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC%/6 or PC7 (page 8, paragraphs 1 and 2). This meets the limitations of claims 1 and 2. The reference also discloses pharmaceutical composition of that includes compositions with viscous paraffin, fatty acid mono and diglycerides (page 13, paragraph 1) and use of non-aqueous vehicles such as cottonseed oil and other oils (page 14, paragraph 1) that are useful in solubilizing lipid soluble active agents. This meets the limitations of claim 3. Dubois teaches the use of PDX or a construct, variant, analog, peptide, peptidomimetic, salt complex derivative thereof for abnormal wound healing with furin or furin-like inhibitors, therefore, it inherently reduces **scar formation** during healing of wounds (page 8, paragraphs 1 and 2). Dubois also discloses that the aforementioned pharmaceutical composition may be administered orally parenterally, inhalation, rectally or topically (page 12, paragraph 2). According to the definition available for "topical" in the website: http://encarta.msn.com/encnet/features/dictionary/DictionaryResults.aspx?refid=1861720920,

the term "topical" means "[d]escribes drugs or medications that are applied **directly** to the surface of the part of the body being treated". Hence meets the limitations of instant claims 1, 25 and 26.

Although, the reference of Dubois discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity, it does not specifically disclose the elected species decanoyl-RVKR-cmk.

Pearton, et al., discloses the elected species decanoyl-RVKR-cmk. The cited reference of Pearton teaches that the decanoyl-RVKR-cmk as a peptide PC inhibitor inhibits the cleavage of Notch-1, a receptor important in cell fate determination and is found throughout the epidermis (Abstract). The decanoyl-RVKR-cmk is a chloromethylketone peptide. The reference teaches that a protease family that has been implicated in processing and differentiation in a number of tissues is the Proprotein Convertase (PC) family. Furin (also known as PACE), PACE4, PC5/6 or PC7/8 belongs to this proprotein Convertase (PC) family. The PC enzymes recognize basic motifs, cleaving after paired basic residues (PC2 and PC1/3) or after a canonical RX(R/K)R motif (furin and PACE4). Furin has been shown to process a wide variety of substrates including receptors, growth factors, hormones, plasma proteins, matrix metalloproteinases and extracellular matrix components. Several proteins relevant to keratinocyte development have been shown to be substrates for PC processing or contain potential PC cleavage sites that include receptors such as Notch-1 receptors (page 193 column 2, and 194 column 1). Pearton, et al., tested the inhibition of furin with decanoyl-RVKR-cmk in the processing of Notch-1 receptor that has a key role in the cell fate determination and patterning. The inhibition of the processing

of Notch-1 from the precursor form (220kDa) to the functional 120 kDa was observed indicating the inhibition of the furin, which is a proprotein Convertase (page 199, column 2, paragraph 2). The fact that decanoyl-RVKR-cmk is a peptide choromethylketone and inhibits furin, which is a proprotein Convertase meets, the limitations of claims 4 and 5. The reference of Pearton teaches that the Decanoyl-RVKR-CMK is a **cell permeable** PC inhibitor (page 199, column 2, paragraph 2).

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Dubois and Pearton, et al., in order to develop a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder, because Dubois teaches the composition of protein based protease inhibitors for furin and furin-like activity and Pearton teaches that decanoyl-RVKR-cmk inhibits the activity of furin a PC enzyme. The motivation comes from the fact that Dubois teaches use of PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others and Pearton teaches that decanoyl-RVKR-cmk is a peptide choromethylketone and inhibits furin which is a proprotein Convertase that inhibits the processing of Notch-1 receptor that is involved in the cell fate determination and patterning of epidermis. Also, that the Decanoyl-RVKR-CMK is a cell permeable PC inhibitor. Cited reference of Pearton also teaches that proprotein convertases (PCs) may play multiple roles during the differentiation of cells within the epidermis (page 202, column 1, paragraph 2). There

would have been reasonable expectation of success given the fact that Dubois taught that analogs, peptides and peptide mimetics of PDX could be used in formulations for the inhibition of furin or furin-like protease activity and the fact that the elected species of the instant invention was used in the inhibition of furin to inhibit the processing of Notch-1 receptor that is key in the cell fate determination and patterning of epidermis. The fact the Decanoyl-RVKR-CMK is a cell permeable PC inhibitor, one would have reasonable expectation to use this analog of the furin inhibitor as it has been shown to be a good cell permeation property compared to other analogs, variants, salts or derivatives thereof.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue that "[t]his basis for rejection assumes that Dubois teaches the invention as claimed in claims 1-3, which has been demonstrated not to be the case above. Thus, the rejection for obviousness fails for this reason alone.

However, it fails for an additional reason. There is no teaching or suggestion in either Pearton or Dubois that the furin inhibitor must be one that inhibits the formation of active TGF-β at the site of wound healing. It may be true that the PDX compound described in Dubois does inhibit TGF Claims 4 and 5 were rejected as assertedly obvious over Dubois in further view of Pearton (Exp. Dermatol., (2001) 10:193-203. This basis for rejection assumes that Dubois teaches the invention as claimed in claims 1-3, which has been demonstrated not to be the case above".

Applicant's arguments filed 8/5/08 have been fully considered but they are not persuasive. Applicant's argument that there is no teaching or suggestion in either Pearton or Dubois that the furin inhibitor must be one that inhibits the formation of active TGF-β at the site of wound healing is not persuasive. Because, the limitation "wherein the furin inhibitor inhibits TGF-β activation" is an inherent function of furin inhibitors. Topical application of furin or furin-like inhibitor as disclosed in Dubois meets the limitations of instant claim 1. Since the furin inhibitor is applied topically (**directly**, please see the definition provided in the rejection above for the term 'topical') to wound site, it is inherent that the compound exhibits inhibition of TGF-β activation. Pearton reference as clearly stated in the rejection was used indicate that the elected species Decanoyl-RVKR-CMK is a well known furin inhibitor. Furthermore, it should be noted that KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (*See Ex Parte Smith*, USPQ2d, slip op. 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR v. Teleflex*, 82 USPQ2d 1396). Hence the rejection under obviousness is proper and maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as stated in the office action dated 6/22/07 and reiterated below. The rejection has been modified to reflect the amendments made to claim 1. Please note that the response to applicant's argument is addressed at the end of the reiterated rejection.

The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, because, in the instant application, applicants claim a method for reducing scar formation during the healing of wounds and the claims as recited include any and all furin classes of inhibitors for reducing normal scarring response during healing of wounds.

In the instant application, applicants claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include:

a. Actual reduction to practice;
b. Disclosure of drawings or structural chemical formulas;
c. Sufficient relevant identifying characteristics such as:

i. Complete structure,
ii. Partial structure,
iii. Physical and/or chemical properties or
iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;

d. Method of making the claimed invention;
e. Level of skill and knowledge in the art and
f. Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

The claims as recited and as previously stated include any and all furin inhibitors. The specification lists several classes of compounds as Convertase inhibitors (page 9 of the specification) that in turn contain many species of inhibitors. The classes of compounds and species within the disclosed classes belong to different classes of biomolecules such as DNA, proteins, peptides, hormones, ribozymes, antisense DNA and organic molecules. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. However, in the instant case, the specification does not provide examples or structural characteristics associated with all these classes or species of inhibitors. The specification only provides the structural features of two inhibitors decanoly-RVKR-cmk and hexa-arginine. Therefore, the "furin inhibitors" as claimed in the present invention represent innumerable chemical compounds and molecules with widely varying structural characteristics that belong to different classes of compounds as mentioned above. The specification is silent on the

representative examples for each of these classes of compounds in terms of structural features, chemical formulae and/or structure-function relations. Therefore the claims as recited and the specification as disclosed is inadequate in providing support for the invention as recited.

The claim 3 recites that the inhibitor is lipid soluble. The specification does not provide adequate description as to the nature or structural features that constitute a lipid soluble molecule. Specification lacks written description to support this claim. There are innumerable numbers of molecules that are lipid soluble in literature. A peptide that comprises of only hydrophobic amino acids or a peptide modified with a lipophilic moiety is lipid soluble molecule. Any molecule attached to a polyalkyl hydrocarbon chain will also be lipid soluble molecule. The claim as recited and specification as disclosed neither provides a proper definition nor any structural characteristics associated with the inhibitor that is lipid soluble.

The claim 4 of instant application recites that the inhibitor is a peptidyl chloromethylketone having a peptide moiety that mimics at least one Convertase enzyme site. To begin with, Convertase enzyme families themselves are classified according to their distribution in various tissues and are classified into several subgroups (page 2 of Dubios reference). Mere recitation of peptidyl chloromethylketone having a peptide moiety that mimics at least one Convertase enzyme site does not provide adequate written description support to the invention without providing proper structural feature and chemical formulae that represents structure for the peptide analogs and the associated Convertase enzyme that the peptide inhibits.

Therefore, the claim(s) as recited contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicants argue that the "[b]asis for this rejection appears to be that there is insufficient structural definition of the compounds included within the invention.

However, in view of the wide variety of furin inhibitors that are known in the art and in view of the description in the application which permits the ordinary practitioner to test which of these have the desired property of inhibiting TGF-β activation, applicants respectfully submit that the written description requirement is met. For example, furin inhibitors are disclosed in:

> Lu, W., et al., J. Biol. Chem. (1993) 268:14583-14585;
> Jean, F., et al., Biochem. J. (1995) 307:689-695;
> Dahlen, J. R., et al., J. Biol. Chem. (1998) 273:1851-1854; and
> Basak, A., et al., Biochem. J. (1999) 338:107-113.

Copies of these documents are enclosed for the convenience of the Office. Thus, there was a plethora of candidate furin inhibitors available in the art at the time the invention was made.

The application describes, on page 24, a method for assessing the formation of active TGFI3 in platelets using the PAI luciferin bioassay described by Abe, et al., Anal. Biochem. (1994) 216:276-284. In this assay, TGFI3 causes expression of luciferase in genetically modified mink lung epithelial cells, which then cleaves luciferin to provide a luminescent reaction. Thus, one need only supply the art-known furin inhibitor candidate to the compositions subjected to this assay as described on page 24 in order to confirm the ability to activate TGF-β".

Applicant's arguments filed 8/5/08 have been fully considered but they are not persuasive. Applicants arguments that a wide variety of furin inhibitors are known in the art and in view of the description in the application which permits the ordinary practitioner to test which

of these have the desired property of inhibiting TGF-β activation, applicants respectfully submit that the written description requirement is met. For example, furin inhibitors are disclosed in: a) Lu, W., et al., J. Biol. Chem. (1993) 268:14583-14585; b) Jean, F., et al., Biochem. J. (1995) 307:689-695; c) Dahlen, J. R., et al., J. Biol. Chem. (1998) 273:1851-1854; and d) Basak, A., et al., Biochem. J. (1999) 338:107-113 provide written description to the instant invention is not persuasive. As stated in the rejection above, the furin inhibitors belongs to different classes of compounds such as DNA, proteins, peptides, hormones, ribozymes, antisense DNA and organic molecules. By merely mentioning that the prior art discloses a plethora of compounds that are furin inhibitors and there are methods available in the prior art to screen them for their biological activity does not provide written description. The claims as recited and applicant's specification as disclosed is inadequate to in terms of providing structure-function relationship between the furin-inhibitor and the inhibition of TGF-β activation. Although, the specification provides a method for screening for the potential candidates for functional characteristics, one of ordinary skill in the art would be burdened to practice the invention as claimed considering the vastness of the genus of 'furin inhibitors' in terms of structural variability in the different classes of compounds as afore-mentioned. Applicants have shown only two compounds hex-arginine and decanoly-RVKR-cmk that belongs to the class of peptides.

Therefore, the rejection as stated above is proper and is maintained.

New grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 23-26 are rejected under 35 USC 102(b) as being anticipated by WO 00/40227 (Noble).

In the instant application, applicants claim a method for reducing scar formation during the healing of at least one wound in a subject who has incurred injuries or in a subject who will be inflicted with at least one surgical wound at a known site, comprising applying a furin inhibitor **directly** to the site of a wound, wherein said furin inhibitor inhibits TGF-β activation.

Noble discloses that dermal scarring occur following dermal injury fro excessive accumulation of fibrous tissue (extra-cellular matrix (ECM)) made up of collagen, proteoglycan and fibronectins at the wound site and TGF-β is believed to induce the deposition of fibrous matrix at the wound site (page 2, lines 8-12). Noble discloses a method of using agents that directly or indirectly inhibit TGF-β activity wherein the direct inhibitors are TGF-β antibodies, proteoglycans (page 10, lines 12-16) and use of agents such as serine proteases including plasmin, metalloproteases, etc., (page 10, lines 19-22). This reads on instant claims 1 and 2. Noble also discloses that medical conditions that are associated with excess accumulation ECM i.e., scar formation at wound site (page 14, lines 6-15) and include scars resulting from spinal cord injury, glaucoma surgery, burns, surgery, etc., (page 14, lines 25-31). This reads on instant claims 23 and 24. The mode of administration of TGF-β inhibitory agents include parenteral

(intravenous, intradermal, intramuscular, etc.), oral, intranasal and topical preparations (page 28, lines 4-11). This reads on instant claims 25 and 26.

Hence Noble anticipates instant invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11153897 in view of WO 00/40227 (Noble).

In the instant application, applicants claim a method for reducing scar formation during the healing of at least one wound in a subject who has incurred injuries or in a subject who will be inflicted with at least one surgical wound at a known site, comprising applying a furin inhibitor **directly** to the site of a wound, wherein said furin inhibitor inhibits TGF-β activation.

Claim 1 of the copending application is drawn to a method of inhibiting scar tissue formation during healing of wound comprising a step of administering an agent that specifically neutralizes the fibrotic activity of TGF-β.

Noble discloses that dermal scarring occur following dermal injury from excessive accumulation of fibrous tissue (extra-cellular matrix (ECM)) made up of collagen, proteoglycan and fibronectins at the wound site and TGF-β is believed to induce the deposition of fibrous matrix at the wound site (page 2, lines 8-12). Noble discloses a method of using agents that directly or indirectly inhibit TGF-β activity wherein the direct inhibitors are TGF-β antibodies, proteoglycans (page 10, lines 12-16) and use of agents such as serine proteases including plasmin, metalloproteases, etc., (page 10, lines 19-22). Hence reads on claim 1 of copending applications 10,522,222 and 11,153,897.

Hence Noble anticipates the inventions of copending applications 10,522,222 and 11,153,897.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654